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PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,069	BRASLAWSKY ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,29,38-40 and 51-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,29,38-40,51-59,61, 63-72, 74 and 76-79* is/are rejected.

7)☒ Claim(s) *60,62,73 and 75* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19, 21-28, 30-37, 41-50 have been cancelled.

Claims 20, 29 and 38 have been amended.

Claims 51-79 have been added.

2. Claims 20, 29, 38-40 and 51-79 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Objection.

Objections/Rejections Withdrawn

5. The objections to the specification for containing the relationship between the instant application and the provisional applications for which a priority benefit is sought and for not containing the updated status of the disclosed USSNs are withdrawn in view the amendments to the specification.

6. The objection to claim 37 as being drawn to non-elected inventions is withdrawn in view of the cancellation of the claim.

7. The rejections of claims 21-34 and 36-40 (parts a-f) under 35 U.S.C. 112, second paragraph, as being indefinite are withdrawn in view of the amendments to the claims.

8. The rejection of claims 20-24, 26-32, 34 and 38-40 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of applicant's arguments and the amendments to the claims.

9. The rejection of claims 30-34 and 36 under 35 U.S.C. 102(a) as being anticipated by Goel et al [a] is withdrawn in view of the cancellation of the claims.

10. The rejection of claims 29-34 and 36-40 under 35 U.S.C. 102(a) as being anticipated by Goel et al [b] is withdrawn in view of applicant's arguments and the amendments to the claims.

11. The rejection of claims 29-34 and 36-40 under 35 U.S.C. 102(b) as being anticipated by Pavlinkova et al [a] is withdrawn in view of applicant's arguments and the amendments to the claims.

12. The rejection of claims 29-34 and 36-40 under 35 U.S.C. 102(b) as being anticipated by Pavlinkova et al [b] is withdrawn in view of applicant's arguments and the amendments to the claims.

13. The rejection of claims 30-34 and 36-37 under 35 U.S.C. 102(b) as being anticipated by Mezes et al is withdrawn in view of the cancellation of the claims.

14. The rejection of claims 30-33 and 36-37 under 35 U.S.C. 102(b) as being anticipated by Slavin-Chiorini et al is withdrawn in view of the cancellation of the claims.

15. The rejection of claims 21-28, 30-34 and 36 under 35 U.S.C. 103(a) as being unpatentable over Goel et al [a] is withdrawn in view of the cancellation of the claims.

16. The rejection of claims 20-34 and 36-40 under 35 U.S.C. 103(a) as being unpatentable over Goel et al [b] is withdrawn in view of applicant's arguments and the amendments to the claims.

17. The rejection of claims 20-34 and 36-40 under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al [a] or Pavlinkova et al [b] is withdrawn in view of applicant's arguments and the amendments to the claims.

18. The rejection of claims 21-28, 30-34 and 36-37 under 35 U.S.C. 103(a) as being unpatentable over Mezes et al in view of Anderson et al is withdrawn in view of the cancellation of the claims.

19. The rejection of claims 21-28, 30-34 and 36-37 under 35 U.S.C. 103(a) as being unpatentable over Slavin-Chiorini et al is withdrawn in view of the cancellation of the claims.

Response to Arguments

20. The rejection of claims 29, 38-40 and applied to newly added claims 64 and 72 under 35 U.S.C. 102(a) as being anticipated by Goel et al [a] is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Goel et al [a] do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides and the antibody of Goel et al [a] does not have more than two sets of light and heavy chains. In response to this argument Goel et al [a] teach a teravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides and the antibodies are non-covalently associated and the tetravalent

antibody binds TAG-72 and is labeled with the radioisotopes ^{125}I and ^{131}I (see Fig. 1 and pages 6965 and 6966, left columns).

Therefore, the rejection of claims 29, 38-40, 64 and 72 under 35 U.S.C. 102(a) as being anticipated by Goel et al [a] is maintained.

21. The rejection of claims 29 and applied to newly added claims 64-65 and 72 under 35 U.S.C. 102(b) as being anticipated by Mezes et al is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Mezes et al do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides. In response to this argument Mezes et al teach multivalent scFvs which comprises two or more scFvs, wherein each scFv comprises two or more light chain variable domains and two or more heavy chain variable domains (see page 2 and Figure 1) and the multivalent antibody binds the same or different antigens (i.e., different epitopes) and preferably binds TAG-72 (i.e., same epitope) (see pages 4-5). As a property is inherent to a product, the multivalent scFvs comprising two or more scFvs wherein each scFv comprises two or more light chain variable domains and two or more heavy chain variable domains would necessarily be associated non-covalently. Further, the multivalent scFvs of Mezes et al would necessarily be minimally tetravalent because each scFv in the mutlimer comprises at least two VH-VL chains and hence two

antigen-binding sites. Thus, a multimer comprising at least two scFvs would have at least four antigen-binding sites (i.e., tetravalent).

Therefore, the rejection of claims 29, 64-65 and 72 under 35 U.S.C. 102(b) as being anticipated by Mezes et al is maintained.

22. The rejection of claims 29, 38-40 and applied to newly added claims 64, 70 and 72 under 35 U.S.C. 102(b) as being anticipated by Slavin-Chiorini et al is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Slavin-Chiorini et al do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides. In response to this argument Slavin-Chiorini et al teach a CH2 domain deleted dimeric antibody that binds TAG-72 (see Figure 1). As evidenced by the specification at page 7, modified antibodies in which the CH2 region has been deleted spontaneously assemble to form stable tetravalent antibodies held together by non-covalent interactions. Therefore, the CH2 domain deleted dimeric antibody of Slavin-Chiorini would necessarily spontaneously assemble into a stable tetravalent antibody held together by non-covalent interactions as this is a property of the CH2 deleted antibody taught in the prior art. For example in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); the following was noted. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a

scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

Therefore, the rejection of claims 29, 38-40, 64, 70 and 72 under 35 U.S.C. 102(b) as being anticipated by Slavin-Chiorini et al is maintained.

23. The rejection of claims 20, 29, 38-40 and applied to newly added claims 51, 59, 63-64 and 72 under 35 U.S.C. 103(a) as being unpatentable over Goel et al [a] is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Goel et al [a] do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides and the antibody of Goel et al [a] does not have more than two sets of light and heavy chains. In response to this argument and as discussed above, Goel et al [a] teach a teravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides and the antibodies are non-covalently associated and the tetravalent antibody binds TAG-72 and is labeled with the radioisotopes ^{125}I and ^{131}I (see Fig. 1 and pages 6965 and 6966, left columns). Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the reference. Therefore, the reference reads on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or

predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03).

Therefore, the rejection of claims 20, 29, 38-40, 51, 59, 63-64 and 72 under 35 U.S.C. 103(a) as being unpatentable over Goel et al [a] is maintained.

24. The rejection of claims 20, 29, 38-40 and applied to newly added claims 51-52, 59, 63-65, 70 and 72 under 35 U.S.C. 103(a) as being unpatentable over Mezes et al in view of Anderson et al is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Mezes et al do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides and the antibody of Mezes et al does not have more than two sets of light and heavy chains. In response to this argument and as discussed above, Mezes et al teach multivalent scFvs which comprises two or more scFvs, wherein each scFv comprises two or more light chain variable domains and two or more heavy chain variable domains (see page 2 and Figure 1) and the multivalent antibody binds the same or different antigens (i.e., different epitopes) and preferably binds TAG-72 (i.e., same epitope) (see pages 4-5). As a property is inherent to a product, the multivalent scFvs comprising two or more scFvs wherein each scFv comprises two or more light chain variable domains and two or more heavy chain variable domains would necessarily be associated non-covalently. Further, the multivalent scFvs of Mezes et al

would necessarily be minimally tetravalent because each scFv in the mutlimer comprises at least two VH-VL chains and hence two antigen-binding sites. Thus, a multimer comprising at least two scFvs would have at least four antigen-binding sites (i.e., tetravalent). Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the reference. Therefore, the reference reads on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03).

Therefore, the rejection of claims 20, 29, 38-40, 51-52, 59, 63-65, 70 and 72 under 35 U.S.C. 103(a) as being anticipated by Mezes et al in view of Anderson et al is maintained.

25. The rejection of claims 20, 29, 38-40 and applied to newly added claims 51, 57-59, 63-64 and 70-72 under 35 U.S.C. 103(a) as being unpatentable over Slavin-Chiorini is maintained.

The response filed 2/10/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that as amended, Slavin-Chiorini et al do not teach the claimed invention, wherein two antibodies are non-covalently associated to form a tetravalent antibody dimer that comprises four heavy chain polypeptides and four light chain polypeptides. In response to this argument and as discussed above, Slavin-Chiorini et al teach a CH2 domain deleted dimeric antibody that binds TAG-72 (see

Figure 1). As evidenced by the specification at page 7, modified antibodies in which the CH2 region has been deleted spontaneously assemble to form stable tetravalent antibodies held together by non-covalent interactions. Therefore, the CH2 domain deleted dimeric antibody of Slavin-Chiorini would necessarily spontaneously assemble into a stable tetravalent antibody held together by non-covalent interactions as this is an inherent property of the CH2 deleted antibody taught in the prior art. For example in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); the following was noted. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the reference. Therefore, the reference reads on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03).

Therefore, the rejection of claims 29, 38-40, 51, 57-59, 63-64 and 70-72 under 35 U.S.C. 103(a) as being anticipated by Slavin-Chiorini et al is maintained.

New Grounds of Objections/Rejections

26. Claims 54 and 67 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding

site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species CC49, CC83, CC46, CC92, CC30, CC11 and CC15.

The specification lacks complete deposit information for the deposit of anti-TAG-72 antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15. It is unclear whether antibodies possessing the identical properties of antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

Applicant's referral to the deposit of antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15 on pages 13-14 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15 is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

27. Claims 20, 29, 38-40, 51, 53-54, 59, 63-64, 66-67, 72 and 76-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goel et al [a] (cancer research, 60:6964-6971, 15 December 2000, Ids reference XR) in view of Anderson et al (U.S. Patent 6,348,581 B1, priority at least to 2/18,1998, cited previously) and Thorpe et al (U.S. Patent 6,342,219 B1, 4/28/1999).

The claims are drawn to a dimeric antibody that binds TAG-72 and comprises two antibodies that are non-covalently associated to form a tetravalent antibody dimer, wherein each of the antibodies in the dimer comprises two antibody heavy chain polypeptides and two antibody light chain polypeptides, and has two antigen-binding sites, wherein a CH2 domain is deleted from each of the four antibody heavy chain polypeptides in the dimeric antibody and the dimeric antibody is a humanized antibody comprising the non-human CDRs from a TAG-72 antibody selected from CC49, CC83, CC46, CC92, CC30, CC11 and CC15 and each antibody in the dimeric antibody binds the same epitope and the antibody is conjugated to a cytotoxic agent. The claims are also drawn to a kit useful for the treatment of a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder may be colon cancer, the kit comprising said dimeric antibody that binds TAG-72 and a label or insert indicating that said dimeric antibody may be used to treat neoplastic disorder. The intended use of the

claimed kit for the treatment of a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder may be colon cancer is given no patentable weight (MPEP 2111.03).

Goel et al [a] have been described supra. Goel et al [a] does not specifically teach a humanized TAG-72 dimeric antibody or conjugating the dimeric antibody to the recited cytotoxic agents. These deficiencies are made up for in the teachings of Anderson et al and Thorpe et al.

Anderson et al teach humanized antibodies that bind TAG-72 and are derived from antibodies CC49, CC83, CC46, CC92, CC30, CC11 or CC15 and humanized antibodies are advantageous over murine antibodies because they have reduced immunogenicity (i.e., reduced HAMA response) in human patients (see column 8, lines 18-44). Anderson also teaches that the humanized antibodies may be conjugated with various cytotxic agents such as pseudomonas endotoxin, ricin, abrin, methotrexate, daunorubicin, doxorubicin and anti-proliferative agents (see column 15, lines 22-39).

Thorpe et al teach antibody conjugates for cancer therapy comprising anti-tumor drugs, cytokines, antimetabolites, alkylating agents, hormones, toxins, prodrugs and chemotherapeutic agents (see columns 75-76, 88-90, 113-118 and 125-127).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized anti-TAG-72 tetrameric antibody dimer and to have conjugated a cytotoxic agent to the humanized anti-TAG-72 tetrameric antibody dimer for human cancer therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-TAG-72 tetrameric antibody dimer and to have conjugated a cytotoxic agent to the humanized anti-TAG-72 tetrameric antibody dimer for human cancer therapy in view of Goel et al [a] and Anderson et al and Thorpe et al because Goel et al [a] teach a TAG-72 specific tetravalent antibody dimer, wherein each chain in the dimer contains two heavy chain variable regions and two light chain variable regions (i.e., comprises four heavy chain polypeptides and four light chain polypeptides) and the two chains are non-covalently associated and the TAG-72 specific tetravalent antibody dimer has higher avidity and prolonged pharmacokinetics in blood relative to a divalent scFv ($sc(Fv)_2$) and IgG and Anderson et al teach that humanized anti-TAG-72 antibodies including CC49, CC83, CC46, CC92, CC30, CC11 and CC15 and humanized antibodies are advantageous over murine antibodies because they have reduced immunogenicity (i.e., reduced HAMA response) in human patients and Anderson et al and Thorpe et al teach various antibody conjugates comprising a cytotoxic agent for cancer immunotherapy. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to humanize the TAG-72 specific tetravalent antibody dimer to reduce HAMA responses in human cancer patients and according to Goel et al [a] the gain in avidity resulting from multivalency along with an improved half-life makes the tetravalent antibody dimer an important reagent for cancer therapy. Thus, a humanized TAG-72 specific tetravalent antibody dimer has distinct advantages over murine, divalent and IgG antibodies such

as increased avidity and improved half-life, which would also be advantageous for delivering various cytotoxic agents conjugated to the antibody for in vivo cancer therapy. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a humanized TAG-72 tetrameric antibody dimer and to have conjugated a cytotoxic agent to the humanized TAG-72 tetrameric antibody dimer for human cancer therapy in view of Goel et al [a] and Anderson et al and Thorpe et al.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03). It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

28. Claims 20, 29, 38-40, 51, 53-59, 61, 63-64, 66-72, 74 and 76-79 under 35 U.S.C. 103(a) as being unpatentable over Slavin-Chiorini et al (International Journal of Cancer, 53:97-103, 1993, cited previously) as evidenced by the specification in view of Anderson et al (U.S. Patent 6,348,581 B1, priority at least to 2/18/1998) and Thorpe et

al (U.S. Patent 6,342,219 B1, 4/28/1999) and Gillies et al (Human Antibodies and Hybridomas, 1(1):47-54, 1990).

The claims have been described supra.

Claims 55 and 68 recite a chimeric antibody comprising non-human light and heavy chain variable regions and human antibody constant regions.

Claims 56, 61, 69, 71 and 74 recite wherein the antibody dimer comprises an antibody heavy chain polypeptide in which a CH3 domain is fused directly to the hinge region.

Slavin-Chiorini et al teach a CH2 domain deleted antibody that binds TAG-72 (see Figure 1) and would necessarily exist as a dimeric antibody wherein the two antibodies are non-covalently associated as evidenced by the specification. As evidenced by the specification at page 7, modified antibodies in which the CH2 region has been deleted spontaneously assemble to form stable tetravalent antibodies held together by non-covalent interactions. Therefore, the CH2 domain deleted dimeric antibody of Slavin-Chiorini et al would necessarily spontaneously assemble into a stable tetravalent antibody held together by non-covalent interactions as this is an inherent property of the CH2 deleted antibody of the prior art. For example, in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); the following was noted. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. Salvin-Chiorini et al do not

specifically teach a chimeric or humanized antibody, wherein the humanized antibody comprises the non-human CDRs selected from one of murine antibodies CC49, CC83, CC46, CC92, CC30, CC11 and CC15, or wherein the antibody dimer comprises a heavy chain polypeptide in which an amino acid spacer is inserted in place of the deleted CH2 domain. These deficiencies are made up for in the teachings of Anderson et al and Thorpe et al.

Anderson et al have been described supra. Anderson et al also teaches chimeric antibodies comprising heavy and light chain variable regions of a non-human antibody that bind TAG-72 and human constant regions (see columns 2-3 and 7).

Thorpe et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an anti-TAG-72 CH2 domain deleted antibody and to have conjugated a cytotoxic agent to the anti-TAG-72 CH2 domain deleted antibody for human cancer therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced an anti-TAG-72 CH2 domain deleted antibody and to have conjugated a cytotoxic agent to the anti-TAG-72 CH2 domain deleted antibody for human cancer therapy in view of Slavin-Chiorini et al and Anderson et al and Thorpe et al and Gillies et al because Slavin-Chiorini et al teach a CH2 domain deleted antibody that binds TAG-72 (see Figure 1) and would necessarily exist as a dimeric antibody wherein the two antibodies are non-covalently associated as evidenced by the specification (see page 7)

and Anderson et al teach chimeric anti-TAG-72 antibodies and humanized anti-TAG-72 antibodies including CC49, CC83, CC46, CC92, CC30, CC11 and CC15 and chimeric and humanized antibodies are advantageous over murine antibodies because they have reduced immunogenicity (i.e., reduced HAMA response) for human therapy and Anderson et al and Thorpe et al teach various antibody conjugates comprising a cytotoxic agent for cancer immunotherapy. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to chimerize and humanize the anti-TAG-72 CH2 domain deleted antibody of Slavin-Chiorini et al to reduce HAMA responses in cancer patients and according to Slavin-Chiorini et al the anti-TAG-72 CH2 domain deleted antibody has a significantly faster plasma clearance rate and more rapid tumor targeting as compared the intact complete antibody and lack of metabolic uptake in normal tissues (see pages 100-102). Additionally, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced an anti-TAG-72 CH2 domain deleted antibody wherein the CH3 domain is fused directly to the hinge region for human cancer therapy in view of Slavin-Chiorini et al and Anderson et al and Thorpe et al and Gillies et al because Gillies et al teach a CH2 deleted antibody wherein the CH3 domain is fused directly to the hinge region and the antibody had increased binding activity and a shorter half-life in vivo (see Figure 1 and page 52, left column). Thus, a chimeric or humanized anti-TAG-72 CH2 domain deleted antibody (regardless of whether the CH2 domain is replaced with a flexible glycine-serine linker or the CH3 is directly fused to the hinge region) has distinct advantages over the intact

complete anti-TAG-72 antibody such as faster plasma clearance rate and more rapid tumor targeting, which would also be advantageous for delivering various cytotoxic agents conjugated to the antibody for in vivo cancer therapy. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced an anti-TAG-72 CH2 domain deleted antibody and to have conjugated a cytotoxic agent to the anti-TAG-72 CH2 domain deleted antibody for human cancer therapy in view of Slavin-Chiorini et al and Anderson et al and Thorpe et al and Gillies et al.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03). It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

29. Claims 60, 62, 73 and 75 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at

(571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER